

23546-08072/US (BIOL0002US)
SEQUENCE LISTING

<110> George Tachas
Kenneth W. Dobie
Ravi Jain
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Mark Andrew Heffernan

<120> MODULATION OF GROWTH HORMONE RECEPTOR EXPRESSION AND INSULIN LIKE
GROWTH FACTOR EXPRESSION

<130> BIOL0002US

<150> 60/451,455

<151> 2003-02-28

<160> 268

<210> 1
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<400> 1
tccgtcatcg ctcctcaggg

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gtgcgcgcgga gcccgaaatc

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<210> 3

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<212> DNA

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<220>

<223> Antisense Oligonucleotide

<400> 3

atgcattctg cccccaagga

20

<210> 4

<211> 4414

<212> DNA

<213> H. sapiens

<220>

<220>

<221> CDS

<222> (44)...(1960)

<400> 4

ccgcgctctc tgatcagagg cgaagctcgg aggtcctaca ggt atg gat ctc tgg

55

Met Asp Leu Trp

1

cag ctg ctg ttg acc ttg gca ctg gca gga tca agt gat gct ttt tct

103

Gln Leu Leu Leu Thr Leu Ala Leu Ala Gly Ser Ser Asp Ala Phe Ser

5

10

15

20

| | |
|---|-----|
| gga agt gag gcc aca gca gct atc ctt agc aga gca ccc tgg agt ctg | 151 |
| Gly Ser Glu Ala Thr Ala Ala Ile Leu Ser Arg Ala Pro Trp Ser Leu | |
| 25 30 35 | |
| caa agt gtt aat cca ggc cta aag aca aat tct tct aag gag cct aaa | 199 |
| Gln Ser Val Asn Pro Gly Leu Lys Thr Asn Ser Ser Lys Glu Pro Lys | |
| 40 45 50 | |
| ttc acc aag tgc cgt tca cct gag cga gag act ttt tca tgc cac tgg | 247 |
| Phe Thr Lys Cys Arg Ser Pro Glu Arg Glu Thr Phe Ser Cys His Trp | |
| 55 60 65 | |
| aca gat gag gtt cat cat ggt aca aag aac cta gga ccc ata cag ctg | 295 |
| Thr Asp Glu Val His His Gly Thr Lys Asn Leu Gly Pro Ile Gln Leu | |
| 70 75 80 | |
| ttc tat acc aga agg aac act caa gaa tgg act caa gaa tgg aaa gaa | 343 |
| Phe Tyr Thr Arg Arg Asn Thr Gln Glu Trp Thr Gln Glu Trp Lys Glu | |
| 85 90 95 100 | |
| tgc cct gat tat gtt tct gct ggg gaa aac agc tgt tac ttt aat tca | 391 |
| Cys Pro Asp Tyr Val Ser Ala Gly Glu Asn Ser Cys Tyr Phe Asn Ser | |
| 105 110 115 | |
| tcg ttt acc tcc atc tgg ata cct tat tgt atc aag cta act agc aat | 439 |
| Ser Phe Thr Ser Ile Trp Ile Pro Tyr Cys Ile Lys Leu Thr Ser Asn | |
| 120 125 130 | |
| ggt ggt aca gtg gat gaa aag tgt ttc tct gtt gat gaa ata gtg caa | 487 |
| Gly Gly Thr Val Asp Glu Lys Cys Phe Ser Val Asp Glu Ile Val Gln | |
| 135 140 145 | |
| cca gat cca ccc att gcc ctc aac tgg act tta ctg aac gtc agt tta | 535 |
| Pro Asp Pro Pro Ile Ala Leu Asn Trp Thr Leu Leu Asn Val Ser Leu | |
| 150 155 160 | |
| act ggg att cat gca gat atc caa gtg aga tgg gaa gca cca cgc aat | 583 |
| Thr Gly Ile His Ala Asp Ile Gln Val Arg Trp Glu Ala Pro Arg Asn | |

| | | | | |
|---|-----|-----|-----|------|
| 165 | 170 | 175 | 180 | |
| gca gat att cag aaa gga tgg atg gtt ctg gag tat gaa ctt caa tac | | | | 631 |
| Ala Asp Ile Gln Lys Gly Trp Met Val Leu Glu Tyr Glu Leu Gln Tyr | | | | |
| | 185 | 190 | 195 | |
| aaa gaa gta aat gaa act aaa tgg aaa atg atg gac cct ata ttg aca | | | | 679 |
| Lys Glu Val Asn Glu Thr Lys Trp Lys Met Met Asp Pro Ile Leu Thr | | | | |
| | 200 | 205 | 210 | |
| aca tca gtt cca gtg tac tca ttg aaa gtg gat aag gaa tat gaa gtg | | | | 727 |
| Thr Ser Val Pro Val Tyr Ser Leu Lys Val Asp Lys Glu Tyr Glu Val | | | | |
| | 215 | 220 | 225 | |
| cgt gtg aga tcc aaa caa cga aac tct gga aat tat ggc gag ttc agt | | | | 775 |
| Arg Val Arg Ser Lys Gln Arg Asn Ser Gly Asn Tyr Gly Glu Phe Ser | | | | |
| | 230 | 235 | 240 | |
| gag gtg ctc tat gta aca ctt cct cag atg agc caa ttt aca tgt gaa | | | | 823 |
| Glu Val Leu Tyr Val Thr Leu Pro Gln Met Ser Gln Phe Thr Cys Glu | | | | |
| | 245 | 250 | 255 | 260 |
| gaa gat ttc tac ttt cca tgg ctc tta att att atc ttt gga ata ttt | | | | 871 |
| Glu Asp Phe Tyr Phe Pro Trp Leu Leu Ile Ile Ile Phe Gly Ile Phe | | | | |
| | 265 | 270 | 275 | |
| ggg cta aca gtg atg cta ttt gta ttc tta ttt tct aaa cag caa agg | | | | 919 |
| Gly Leu Thr Val Met Leu Phe Val Phe Leu Phe Ser Lys Gln Gln Arg | | | | |
| | 280 | 285 | 290 | |
| att aaa atg ctg att ctg ccc cca gtt cca gtt cca aag att aaa gga | | | | 967 |
| Ile Lys Met Leu Ile Leu Pro Pro Val Pro Val Pro Lys Ile Lys Gly | | | | |
| | 295 | 300 | 305 | |
| atc gat cca gat ctc ctc aag gaa gga aaa tta gag gag gtg aac aca | | | | 1015 |
| Ile Asp Pro Asp Leu Leu Lys Glu Gly Lys Leu Glu Glu Val Asn Thr | | | | |
| | 310 | 315 | 320 | |
| atc tta gcc att cat gat agc tat aaa ccc gaa ttc cac agt gat gac | | | | 1063 |

Ile Leu Ala Ile His Asp Ser Tyr Lys Pro Glu Phe His Ser Asp Asp
325 330 335 340

act gag gaa tca gac aca gac aga ctt cta agc agt gac cat gag aaa 1159
Thr Glu Glu Ser Asp Thr Asp Arg Leu Leu Ser Ser Asp His Glu Lys
360 365 370

tgt tgt gaa cct gac att ctg gag act gat ttc aat gcc aat gac ata 1255
Cys Cys Glu Pro Asp Ile Leu Glu Thr Asp Phe Asn Ala Asn Asp Ile
390 395 400

cat gag ggt acc tca gag gtt gct cag cca cag agg tta aaa ggg gaa 1303
His Glu Gly Thr Ser Glu Val Ala Gln Pro Gln Arg Leu Lys Gly Glu
405 410 415 420

gca gat ctc tta tgc ctt gac cag aag aat caa aat aac tca cct tat 1351
Ala Asp Leu Leu Cys Leu Asp Gln Lys Asn Gln Asn Asn Ser Pro Tyr
425 430 435

cat gat gct tgc cct gct act cag cag ccc agt gtt atc caa gca gag 1399
His Asp Ala Cys Pro Ala Thr Gln Gln Pro Ser Val Ile Gln Ala Glu
440 445 450

aaa aac aaa cca caa cca ctt cct act gaa gga gct gag tca act cac 1447
Lys Asn Lys Pro Gln Pro Leu Pro Thr Glu Gly Ala Glu Ser Thr His
455 460 465

caa gct gcc cat att cag cta agc aat cca agt tca ctg tca aac atc 1495
Gln Ala Ala His Ile Gln Leu Ser Asn Pro Ser Ser Leu Ser Asn Ile
470 475 480

gac ttt tat gcc cag gtg agc gac att aca cca gca ggt agt gtg gtc 1543
Asp Phe Tyr Ala Gln Val Ser Asp Ile Thr Pro Ala Gly Ser Val Val
485 490 495 500

ctt tcc ccg ggc caa aag aat aag gca ggg atg tcc caa tgt gac atg 1591
Leu Ser Pro Gly Gln Lys Asn Lys Ala Gly Met Ser Gln Cys Asp Met
505 510 515

cac ccg gaa atg gtc tca ctc tgc caa gaa aac ttc ctt atg gac aat 1639
 His Pro Glu Met Val Ser Leu Cys Gln Glu Asn Phe Leu Met Asp Asn
 520 525 530

gcc tac ttc tgt gag gca gat gcc aaa aag tgc atc cct gtg gct cct 1687
Ala Tyr Phe Cys Glu Ala Asp Ala Lys Lys Cys Ile Pro Val Ala Pro
535 540 545

cac atc aag gtt gaa tca cac ata cag cca agc tta aac caa gag gac 1735
 His Ile Lys Val Glu Ser His Ile Gln Pro Ser Leu Asn Gln Glu Asp
 550 555 560

att tac atc acc aca gaa agc ctt acc act gct gct ggg agg cct ggg 1783
Ile Tyr Ile Thr Thr Glu Ser Leu Thr Thr Ala Ala Gly Arg Pro Gly
565 570 575 580

aca gga gaa cat gtt cca ggt tct gag atg cct gtc cca gac tat acc 1831
Thr Gly Glu His Val Pro Gly Ser Glu Met Pro Val Pro Asp Tyr Thr
585 590 595

tcc att cat ata gta cag tcc cca cag ggc ctc ata ctc aat gcg act 1879
Ser Ile His Ile Val Gln Ser Pro Gln Gly Leu Ile Leu Asn Ala Thr
600 605 610

gcc ttg ccc ttg cct gac aaa gag ttt ctc tca tca tgt ggc tat gtg 1927
Ala Leu Pro Leu Pro Asp Lys Glu Phe Leu Ser Ser Cys Gly Tyr Val
615 620 625

agc aca gac caa ctg aac aaa atc atg cct tag cctttctttg gtttcccaag 1980
 Ser Thr Asp Gln Leu Asn Lys Ile Met Pro
 630 635

agctacgtat ttaatagcaa agaattgact ggggcaataa cgtttaagcc aaaacaatgt 2040
 ttaaacccttt tttgggggag tgacaggatg gggatatggat tctaaaatgc cttttcccaa 2100
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 aagtatttgt taatttagaa aactttaaag cgtttgaca gatcaactta ccaggcacca 2820
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taatgaaaca aagagttcaa gaaataagtt tttgtttcac agcctataac cagacacata 3180
 ctcatTTTTc atgataatga acagaacata gacagaagaa acaaggTTTT cagtccccac 3240
 agataactga aaattattta aaccgctaaa agaaactttc tttctcacta aatcttttat 3300
 aggatttatt taaaatagca aaagaagaag tttcatcatt ttttacttcc tctctgagtg 3360
 gactggcctc aaagcaagca ttcagaagaa aaagaagcaa cctcagtaat ttagaaatca 3420
 ttttgcaatc ccttaatatc ctaaacaatca ttcatttttg ttgttggttg tggttggtgag 3480
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<213> Artificial Sequence

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<223> PCR Primer

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aagtaggcat tgtccataag gaagtt 26

<210> 7

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<220>

<223> PCR Probe

<400> 7

ccggaaatgg tctcactctg ccaaga

26

<210> 8

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR Primer

<400> 8

gaaggtgaag gtcggagtc

19

<210> 9

<211> 20

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<400> 10

caagcttccc gttctcagcc

20

<210> 11

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<213> M. musculus

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<222> 2636

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ccggcagccg cggggatccc gggctgggtc cacgcggcct gaggcctcgg ctccagcagc 180

ccccaagcgg acacgaaccc gcgttctgtc tcccgaggcg aaactccgag gtctcaggt 239

atg gat ctt tgt cag gtc ttc tta acc ttg gca ctg gca gtc acc agc 287

Met Asp Leu Cys Gln Val Phe Leu Thr Leu Ala Leu Ala Val Thr Ser

1

5

10

15

agc aca ttt tct gga agt gag gct aca cca gct act ctt ggc aaa gct 335

Ser Thr Phe Ser Gly Ser Glu Ala Thr Pro Ala Thr Leu Gly Lys Ala

20

25

30

tcc cca gtt ctg caa aga atc aat cca agc ctg ggg aca agt tct tct 383

Ser Pro Val Leu Gln Arg Ile Asn Pro Ser Leu Gly Thr Ser Ser Ser

35

40

45

gga aag cct cga ttc acc aag tgt cgt tcc cct gaa ctg gag aca ttt 431

Gly Lys Pro Arg Phe Thr Lys Cys Arg Ser Pro Glu Leu Glu Thr Phe

50

55

60

tca tgc tac tgg aca gaa gga gat aat cct gat tta aag acc cca gga 479

Ser Cys Tyr Trp Thr Glu Gly Asp Asn Pro Asp Leu Lys Thr Pro Gly

65

70

75

80

tct att cag ctg tac tat gct aaa agg gaa agc caa cga caa gct gca 527

Ser Ile Gln Leu Tyr Tyr Ala Lys Arg Glu Ser Gln Arg Gln Ala Ala

85

90

95

aga att gct cat gaa tgg acc cag gaa tgg aaa gaa tgc cct gat tat 575

Arg Ile Ala His Glu Trp Thr Gln Glu Trp Lys Glu Cys Pro Asp Tyr

100

105

110

gtc tct gct gga aaa aac agc tgt tac ttc aac tca tca tat acc tcc 623

Val Ser Ala Gly Lys Asn Ser Cys Tyr Phe Asn Ser Ser Tyr Thr Ser

115

120

125

att tgg ata ccc tac tgc atc aag cta act aca aat ggt gat ttg ctg 671

Ile Trp Ile Pro Tyr Cys Ile Lys Leu Thr Thr Asn Gly Asp Leu Leu

130

135

140

gac caa aaa tgt ttc act gtt gac gaa ata gtg caa cct gat cca ccc 719

Asp Gln Lys Cys Phe Thr Val Asp Glu Ile Val Gln Pro Asp Pro Pro

145

150

155

160

att ggc ctc aac tgg act tta cta aac att agt ttg acc ggg att cgt 767

Ile Gly Leu Asn Trp Thr Leu Leu Asn Ile Ser Leu Thr Gly Ile Arg

165

170

175

gga gac atc caa gtg agt tgg caa cca cca ccc aat gca gat gtt ctg 815

Gly Asp Ile Gln Val Ser Trp Gln Pro Pro Pro Asn Ala Asp Val Leu

180

185

190

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| | |
|---|------|
| aag gga tgg ata att ctg gag tat gaa att cag tac aaa gaa gta aat | 863 |
| Lys Gly Trp Ile Ile Leu Glu Tyr Glu Ile Gln Tyr Lys Glu Val Asn | |
| 195 200 205 | |
| | |
| gaa tca aaa tgg aaa gtg atg ggc cct ata tgg tta aca tac tgt cca | 911 |
| Glu Ser Lys Trp Lys Val Met Gly Pro Ile Trp Leu Thr Tyr Cys Pro | |
| 210 215 220 | |
| | |
| gtg tac tca ttg aga atg gat aaa gaa cat gaa gtg cgg gtg aga tcc | 959 |
| Val Tyr Ser Leu Arg Met Asp Lys Glu His Glu Val Arg Val Arg Ser | |
| 225 230 235 240 | |
| | |
| aga caa cgg agc ttt gaa aag tac agc gag ttc agc gaa gtc ctc cgt | 1007 |
| Arg Gln Arg Ser Phe Glu Lys Tyr Ser Glu Phe Ser Glu Val Leu Arg | |
| 245 250 255 | |
| | |
| gta ata ttt cct cag acg aac ata ttg gaa gca tgt gaa gaa gat atc | 1055 |
| Val Ile Phe Pro Gln Thr Asn Ile Leu Glu Ala Cys Glu Glu Asp Ile | |
| 260 265 270 | |
| | |
| cag ttt cca tgg ttc tta att att atc ttt gga ata ttt gga gta gca | 1103 |
| Gln Phe Pro Trp Phe Leu Ile Ile Ile Phe Gly Ile Phe Gly Val Ala | |
| 275 280 285 | |
| | |
| gtg atg cta ttt gta gtt ata ttt tca aag cag caa agg att aag atg | 1151 |
| Val Met Leu Phe Val Val Ile Phe Ser Lys Gln Gln Arg Ile Lys Met | |
| 290 295 300 | |
| | |
| ctg att tta ccc cca gtc cca gtt cca aag att aaa ggg att gat cca | 1199 |
| Leu Ile Leu Pro Pro Val Pro Val Pro Lys Ile Lys Gly Ile Asp Pro | |
| 305 310 315 320 | |
| | |
| gat ctt ctc aag gga ggg aag ttg gag gag gtg aac acc atc tta ggc | 1247 |
| Asp Leu Leu Lys Gly Gly Lys Leu Glu Glu Val Asn Thr Ile Leu Gly | |
| 325 330 335 | |
| | |
| att cat gat aac tac aaa ccc gac ttc tac aat gat gat tcc tgg gtc | 1295 |
| Ile His Asp Asn Tyr Lys Pro Asp Phe Tyr Asn Asp Asp Ser Trp Val | |
| 340 345 350 | |

| | |
|---|------|
| gag ttc att gag cta gat att gat gaa gca gat gtg gat gag aag act | 1343 |
| Glu Phe Ile Glu Leu Asp Ile Asp Glu Ala Asp Val Asp Glu Lys Thr | |
| 355 360 365 | |
| gaa ggg tct gac aca gac aga ctt cta agc aat gat cat gag aaa tca | 1391 |
| Glu Gly Ser Asp Thr Asp Arg Leu Leu Ser Asn Asp His Glu Lys Ser | |
| 370 375 380 | |
| gct ggt atc ctt gga gca aag gat gat gat tct ggg cgt acc agc tgt | 1439 |
| Ala Gly Ile Leu Gly Ala Lys Asp Asp Asp Ser Gly Arg Thr Ser Cys | |
| 385 390 395 400 | |
| tac gac cct gac att ttg gat act gat ttc cat acc agt gac atg tgt | 1487 |
| Tyr Asp Pro Asp Ile Leu Asp Thr Asp Phe His Thr Ser Asp Met Cys | |
| 405 410 415 | |
| gat ggt acc ttg aag ttt gct cag tca cag aag tta aat atg gaa gct | 1535 |
| Asp Gly Thr Leu Lys Phe Ala Gln Ser Gln Lys Leu Asn Met Glu Ala | |
| 420 425 430 | |
| gat ctc ttg tgc ctt gat cag aag aat ctg aag aac ttg cct tat gat | 1583 |
| Asp Leu Leu Cys Leu Asp Gln Lys Asn Leu Lys Asn Leu Pro Tyr Asp | |
| 435 440 445 | |
| gct tcc ctt ggc tct ctg cat ccc tcc att acc cag aca gta gaa gaa | 1631 |
| Ala Ser Leu Gly Ser Leu His Pro Ser Ile Thr Gln Thr Val Glu Glu | |
| 450 455 460 | |
| aac aag cca cag cca ctt ttg agc agc gaa act gag gca acc cac caa | 1679 |
| Asn Lys Pro Gln Pro Leu Leu Ser Ser Glu Thr Glu Ala Thr His Gln | |
| 465 470 475 480 | |
| ctc gcc tct aca ccg atg agt aat ccc aca tca ctg gca aac att gac | 1727 |
| Leu Ala Ser Thr Pro Met Ser Asn Pro Thr Ser Leu Ala Asn Ile Asp | |
| 485 490 495 | |
| ttt tat gcc caa gta agc gac att aca cca gca ggt ggt gat gtc ctt | 1775 |
| Phe Tyr Ala Gln Val Ser Asp Ile Thr Pro Ala Gly Gly Asp Val Leu | |

| 500 | 505 | 510 | |
|--|-----|-----|------|
| tcc cca ggc caa aag att aag gca ggg ata gcc caa ggc aat acc cag | | | 1823 |
| Ser Pro Gly Gln Lys Ile Lys Ala Gly Ile Ala Gln Gly Asn Thr Gln | | | |
| 515 | 520 | 525 | |
| cgg gag gtg gcc acg ccc tgc caa gaa aat tac agc atg aac agt gcc | | | 1871 |
| Arg Glu Val Ala Thr Pro Cys Gln Glu Asn Tyr Ser Met Asn Ser Ala | | | |
| 530 | 535 | 540 | |
| tac ttt tgt gag tca gat gcc aaa aaa tgc atc gct gtg gcc cgt cgc | | | 1919 |
| Tyr Phe Cys Glu Ser Asp Ala Lys Lys Cys Ile Ala Val Ala Arg Arg | | | |
| 545 | 550 | 555 | 560 |
| atg gaa gcc acg tct tgt ata aaa cca agc ttt aac caa gag gac att | | | 1967 |
| Met Glu Ala Thr Ser Cys Ile Lys Pro Ser Phe Asn Gln Glu Asp Ile | | | |
| 565 | 570 | 575 | |
| tac atc acc aca gaa agc ctt acc act act gcc cag atg tct gag aca | | | 2015 |
| Tyr Ile Thr Thr Glu Ser Leu Thr Thr Thr Ala Gln Met Ser Glu Thr | | | |
| 580 | 585 | 590 | |
| gca gat att gct cca gat gct gag atg tct gtc cca gac tac acc acg | | | 2063 |
| Ala Asp Ile Ala Pro Asp Ala Glu Met Ser Val Pro Asp Tyr Thr Thr | | | |
| 595 | 600 | 605 | |
| gtt cac acc gtg cag tct cca agg ggc ctt ata ctc aac gca act gct | | | 2111 |
| Val His Thr Val Gln Ser Pro Arg Gly Leu Ile Leu Asn Ala Thr Ala | | | |
| 610 | 615 | 620 | |
| ttg cct ttg cct gac aaa aag aat ttt ccc tcc tcg tgt ggt tat gtg | | | 2159 |
| Leu Pro Leu Pro Asp Lys Lys Asn Phe Pro Ser Ser Cys Gly Tyr Val | | | |
| 625 | 630 | 635 | 640 |
| agc aca gac caa ctg aac aaa atc atg cag tag cctttcctat ctttaaattgg | | | 2212 |
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